STATISTICAL ANALYSIS PLAN for BackToBasic

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ABBREVIATIONS

AE	Adverse Event
ASAS	Assessment in SpondyloArthritis International Society
ATC	Anatomical/Therapeutic/Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRP	C-reactive protein
FAS	Full Analysis Set
HSCL	Hopkins Symptom Checklist
ICH	International Council for Harmonisation
LBP	Low Back Pain
MedDRA	Medical Dictionary for Regulatory Activities
MC	Modic Changes
MR	Magnetic resonance
NSAID	Non-Steroidal Anti-Inflammatory Drug
ODI	Oswestry Disability Index
PP	Per Protocol
PROM	Patient Reported Outcome Measure
PT	Preferred Term
RMDQ	Roland-Morris Disability Questionnaire
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor necrosis factor

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1 Introduction

This Statistical Analysis Plan follows the "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" published by Gamble et al (1), complying with the ICH E9 guideline.

1.1 Background and rationale

Low back pain (LBP) nowadays represents the first cause for living with disability, and results in a considerable cost for the affected individuals and for society. Nevertheless, the current standard of care for such condition does not include any patho-anatomic diagnosis, and only provides general treatments or advices, without targeting specific subgroups of patients. Potential subgroups are identified by Modic changes (MC), classified into primary and secondary, and into type 1, 2 and 3. Although the aetiology and pathogenesis of MCs is unclear, it is known that it is characterized by a local inflammatory response in the intervertebral disc and vertebral end-plates. Tumor necrosis factor (TNF) alpha inhibitors, which are used to treat most inflammatory diseases, could therefore prove to be an effective treatment in patients with chronic LBP with concomitant MCs.

1.2 Trial Objectives

1.2.1 Primary Objective

The primary objective of this study is to assess whether a TNF-alpha inhibitor (infliximab) is superior to placebo in terms of change in Oswestry Disability Index (ODI) score from baseline to 5 months in patients with chronic low back pain and Modic changes type 1.

1.2.2 Secondary Objectives

The secondary objectives of this study are to assess the effect of TFN-alpha inhibitor vs placebo in terms of:

- Change from baseline in LBP intensity at 5 months
- Change from baseline in Roland Morris Disability Questionnaire at 5 months
- Change from baseline in health-related quality of life (EQ-5D) at 5 months
- Incidence of AEs and SAEs at 5 months

1.2.3 Exploratory Objectives

The exploratory objectives of this study are to assess the effect of TFN-alpha inhibitor vs placebo in terms of:

- Change from baseline in leg pain intensity at 5 months
- Change from baseline in hours with LBP during the last 4 weeks at 5 months
- Symptom-specific well-being at 5 months
- Change from baseline in days with sick leave at 5 months
- Co-interventions and co-medications at 5 months
- Patients' satisfaction at 5 months
- Global perceived effect at 5 months
- Change from baseline in ODI at 9 months follow-up
- Change from baseline in leg pain intensity at 9 months follow-up

2 Trial Methods

2.1 Trial Design

The BackToBasic study is a randomized, double blind, placebo-controlled, parallel-group, multi-center, single-country, superiority, therapeutic confirmatory phase III study. Treatment allocation is a 1:1 ratio. Patients are randomised to either infliximab (TNF-alpha inhibitor) or placebo. Patients receive treatment four times over a period of 98 days, and are followed up for 9 months after treatment start.

2.2 Randomisation

Eligible patients are allocated in a 1:1 ratio between infliximab and placebo, using a random block randomization procedure, with varying block sizes of 2, 4, 6 and 8, and the randomization is stratified by center and previous participation in the AIM study. Details of block size and allocation sequence generation is provided in a separate document unavailable to those who enroll patients or assign treatment. The randomization process is described in full within the clinical trial protocol. Details of the randomization including the final random allocation list are held securely and unavailable to unauthorized trial personnel, including statisticians, researchers and study workers.

2.3 Sample size

Details about sample size calculation are reported in the protocol. Sample size calculation has been based on the primary endpoint (change in ODI score from baseline to 5 months). To detect a clinically important difference of 10 ODI points in the treatment group compared to placebo, and assuming a standard deviation of 18 ODI points, a total sample size of 104 is required to be 80% certain to reach a statistically significant difference between the treatment arms at the 5% significance level (using Stata 16.0 command power twomeans). Adding 20% to account for potential drop-outs yields 126 patients, 63 in each treatment arm.

2.4 Statistical Framework

2.4.1 Hypothesis Test

This trial is designed to establish the effect of TNF-alpha inhibitor (infliximab) vs placebo in terms of Oswestry Disability Index (ODI) score from baseline to 5 months in patients with chronic low back pain and Modic changes type 1.

- The primary null hypothesis is that there is no difference in the mean change from baseline to 5 months in ODI score (X) between patients receiving the infliximab treatment (T) and patients receiving placebo (P).

$$H_0: X_T - X_P = 0$$

  X_T and X_P indicate the change in ODI score (X) at 5 months from baseline (B) in the treatment and placebo group respectively: $X_T = X_{T,5mont} - B_T$ and $X_P = X_{P,5month} - B_P$.

- The primary alternative hypothesis is there is a non-zero difference in the mean change from baseline to 5 months in ODI score between patients receiving the infliximab treatment (T) and patients receiving placebo (P).

$$H_1: X_T - X_P \neq 0$$

There is only one primary analysis in this trial, therefore no adjustment for multiplicity will be performed. All other efficacy analyses will be regarded as supportive or exploratory.

The primary null hypothesis is evaluated in the full analysis set (FAS), and sensitivity analysis will be performed in the per protocol (PP) analysis set.

2.4.2 Decision Rule

This trial is designed to address a single primary outcome. The primary null hypothesis will be rejected if the two-sided p-value < 0.05 in the primary analysis.

2.5 Statistical Interim Analyses and Stopping Guidance

There will be no interim analyses in this trial.

2.6 Timing of Final Analysis

The main analysis is planned when all patients have received the 9-month follow-up, all data have been entered, verified and validated and the primary database has been locked. Note that this is a change from the timing suggested in the protocol: such change was made to preserve the blinding also in the analysis of the 9-month secondary endpoints.

2.7 Timing of Outcome Assessments

For all clinically planned measures, visits should occur within a window of the scheduled visit. Visit 1, visit 2, visit 3 or visit 4 outside visit window correspond to receiving the infusion outside of the pre-specified window and are regarded a major protocol deviation (see 3.2.2). The target days and visit windows are defined in the protocol as:

Visit Label	**Target Day**	**Definition (Visit window)**
Screening	-30	Within 6 weeks before day 0
V1. Baseline	Day 0 (Randomization)	Day 0
V2	14	Target day ± 3 days
V3	42	Target day ± 5 days
V4	98	Target day ± 7 days
V5	154	Target day ± 7 days
Last study visit*	274	Target day ± 14 days

*The last study visit is defined as the last visit by either physical attendance or by phone call or other sort of web-based communication between the participant and the investigator.

The timelines for PROMs are reported in the protocol (see Appendix 17.2).

3 Statistical Principles

3.1 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the corresponding treatment group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals.

3.2 Adherence and Protocol Deviations

3.2.1 Adherence to Allocated Treatment

Adherence to intervention is defined as four successful infusions, and registered in the eCRF together with dose and time of infusion.

The number and % of participants adhering to the prescribed intervention will be presented in a table for each visit. The patients that are included in the full analysis data set (defined in 3.3) will be used as the denominator to calculate the percentages. Results will be provided by treatment group.

The number and % of successful infusions across the whole study will be summarized by treatment group.

3.2.2 Protocol Deviations

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

- Entering the trial when the eligibility criteria should have prevented trial entry
- Discontinuation of intervention prior to 15 weeks
- Any infusion outside of visit window
- Major change in management or treatment of back pain, e.g. emergency surgery for low back pain or long-term morphine medication, or co-interventions with a suspected substantial impact on back pain outcomes
- Received or used other intervention than allocated

Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the full analysis data set will

be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3.3 Analysis Populations

The Enrolled set will include all patients who have provided informed consent and have been included into the study data base.

The Randomized set will include all patients who have been randomly assigned to a treatment group.

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group having received at least one study treatment infusion after randomisation.

The Safety Analysis Set will include all patients having received at least one study treatment infusion after randomisation (i.e. identical to the FAS).

The Per Protocol Analysis Set (PP) will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy.

The primary null hypothesis is evaluated in the full analysis set, and sensitivity analysis will be performed on the PP analysis set. Safety data will be analysed on the Safety Analysis Set.

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarised and tabulated.

A CONSORT flow diagram will be used to summarise the number of patients who were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis

- randomised and excluded from the primary analysis*

*reasons will be provided.

4.2 Withdrawal/Follow-up

The status of eligible and randomised patients at trial end will be tabulated by treatment group according to

- completed intervention and assessments
- withdrew consent
- lost to follow-up

Time from randomisation to end of study and time from randomisation to withdrawal/lost to follow-up will be summarized by median and IQR, overall and by treatment group.

4.3 Baseline Patient Characteristics

The patient demographics and baseline characteristics will be summarised on the FAS. The variables to be summarised include age in years, gender, BMI, educational level, work status, physical work load, leisure time activity (both hard and light), smoking habits, expectations about treatment effect and characteristics of pain (morning stiffness), as well as emotional distress (mean of 25 questions in the HSCL questionnaire, set as missing if more than 30% unanswered questions), fear-avoidance beliefs about physical activity and work.

Patient demographics and baseline characteristics will be summarised by treatment group and overall using descriptive statistics, i. e. N, mean, standard deviation or mean and IQR for skewed variables for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of treatment difference. Any clinical important imbalance between the treatment groups will be noted.

5 Analysis

5.1 Outcome Definitions

5.1.1 General Definitions and Derived Variables

5.1.1.1 Body Mass Index

Body Mass Index (BMI) = Body weight in kilograms divided by the square of the height in meters.

5.1.1.2 Low Back Pain (LBP) intensity

LBP = (current LBP + worst LBP within the last 2 weeks + usual LBP within the last 2 weeks)/3.

5.1.1.3 Hours with LBP during the last 4 weeks

Hours with LBP = number of days during the last 28 days the participant had experienced LBP (0-28 days) times how many hours awake on a typical day they experienced LBP (0-16 h).

5.1.2 Primary Outcome Definition

The primary outcome is the change in the Oswestry Disability Index (ODI) from baseline to 5 months. This is assessed by the combination of 10 items from the Norwegian validated ODI questionnaire (see appendix 17.3 in the protocol) and measured on a scale from 0 to 100, where 0 indicates no disability and 100 indicates maximum disability. The ODI is calculated as the sum of the scores of the items that are answered, divided by the number of items answered, and multiplied by 0.2 and 100. This is a patient-reported, continuous outcome.

5.1.3 Secondary Outcomes Definitions

5.1.3.1 LBP intensity at 5 months

Low back pain intensity is a patient-reported continuous outcome. It is calculated as the mean of three numeric rating scales (NRSs): the current LBP, the worst LBP within the last 2 weeks, and usual/mean LBP within the last 2 weeks . It ranges from 0 to 10.

5.1.3.2 Roland and Morris Disability Questionnaire (RMDQ) at 5 months

This is a patient-reported continuous outcome. It is defined as the ability to carry out daily activities, and it is assessed by the Norwegian validated version of the RMDQ. The score is calculated as the sum of dichotomous answers to 24 questions, it ranges from 0 to 24.

5.1.3.3 Health-related quality of life (EQ-5D-5L) at 5 months

This is a patient-reported continuous outcome. It is a score ranging from 0 to 1, provided by the EQ-5D-5L questionnaire. The answers are converted into a single score using the UK crosswalk (van Hout et al., (2))

5.1.4 Exploratory Outcomes Definitions

5.1.4.1 Leg pain intensity at 5 months

This is a patient-reported continuous outcome. It is defined as leg pain intensity in the week previous to the reporting. It is measured as NRS and ranges from 0 to 10.

5.1.4.2 Hours with LBP during the last 4 weeks at 5 months

This is a continuous outcome, derived from patient-reported outcomes (see 5.1.1.3). It ranges from 0 to 448, and is calculated by multiplying the number of days during the last 28 days the participant

had experienced LBP (0-28 days) with how many hours awake on a typical day they experienced LBP (0-16 h).

5.1.4.3 Symptom-specific well- being at 5 months

This is a patient-reported ordinal outcome. It is part of the Core Item Measures Index (COMI) for low back pain, and is defined as the answer to the question: "If you had to live the rest of your life with the symptoms you have right now, how would you feel about it?" It is a 5- point Likert scale index, where 1 = 'very satisfied', 2 = 'some satisfied', 3 = 'neither satisfied nor dissatisfied', 4 = 'some dissatisfied' or 5= 'very dissatisfied'.

5.1.4.4 Days with sick leave at 5 months

This is a continuous outcome. It is defined as the number of days where the patient is in sick-leave.

5.1.4.5 Co-interventions at 5 months

It is a dichotomous outcome. It is defined as the use of any pharmacological treatment with indication back pain or non-pharmacological treatment other than the study treatment.

5.1.4.6 Patient's satisfaction at 5 months

This is a patient-reported ordinal outcome. It is a 5- point Likert scale index.

5.1.4.7 Global perceived effect at 5 months

This is a patient-reported ordinal outcome. It is a 7- point Likert scale index.

5.1.4.8 ODI at 9 months

This is defined in the same way as the primary outcome (5.1.2) and collected at the 9 month follow-up.

5.1.4.9 Leg pain intensity at 9 months

This is defined in the same way as 5.1.4.1. and collected at the 9 month follow-up.

5.1.4.10 Perceived treatment at 5 months

It is a continuous outcome. It is calculated as the Bang Blinding Index (3) at 5 months, from the patients' answer to the question "which study medicine do you think you received? (Infliximab /placebo / unsure) ".

5.1.5 Overview of Outcomes

Level	Outcome	Timeframe	Type
Primary	Change from baseline in ODI	5 months	Continuous
Secondary	Change from baseline in LBP intensity	5 months	Continuous

	Change from baseline in RMDQ	5 months	Continuous
	Change from baseline in EQ-5D-5L	5 months	Continuous
Exploratory	Change from baseline in leg pain intensity	5 months	Continuous
	Change from baseline in hours with LBP during the last 4 weeks	5 months	Continuous
	Symptom-specific well- being	5 months	Ordinal
	Change from baseline in days with sick-leave in the last month	5 months	Continuous
	Co-interventions	5 months	Dichotomous
	Patient's satisfaction	5 months	Ordinal
	Global perceived effect	5 months	Ordinal
	Change from baseline in ODI	9 months	Continuous
	Change from baseline in leg pain intensity	9 months	Continuous
	Change from baseline in LBP intensity	9 months	Continuous
	Perceived treatment	5 months	Continuous

5.2 Analysis Methods

5.2.1 Primary Outcome

5.2.1.1 Primary Analysis

The change in ODI from baseline to 5 months will be analysed with a linear mixed model, including the change from baseline in ODI at day 28 (one month visit), day 56 (two month visit), day 91 (three month visit), day 120 (four month visit), day 154 (five month visit, primary) and day 278 (9 month

visit) as a longitudinal outcome. The model will have fixed effects for centre and participation to the AIM study (which were used as stratification factors in the randomization), baseline ODI, visit and treatment group. An interaction between treatment group and visit will also be included. A random intercept for the patient ID will be used to account for repeated measurements. If fewer than 5% of the patients have participated in the AIM study, we expect it to cause problems with the convergence and model fitting, so no adjustment for this variable will be made.

Estimates will be presented with two-sided 95% confidence intervals, and 5% significance level will be used for p-values. The primary estimate will be the treatment effect at 5 months, calculated as average marginal effect from the linear mixed model. The primary analysis will be on the FAS population.

5.2.1.2 Summary Measures

Descriptive statistics will be presented overall and by treatment and will include number of observations, mean value and standard deviation. The change from baseline in ODI will be shown in a graph by visit and treatment group. The estimates of treatment effect will be plotted in a longitudinal graph.

Additionally, we will calculate the relative change in ODI from baseline to 5 months follow-up. We will present the cumulative distribution with 95% confidence bands function by treatment group as recommended by NIH Task Force on Research Standard for Chronic Low Back Pain (3, 4).

5.2.1.3 Assumption Checks and Alternative Analyses

The assumption of normality will be checked via a Q-Q plot. If the normality assumption is violated, alternative methods may include transformations of the variable, or non-parametric models, such as the Wilcoxon rank sum test (without any adjustment).

The presence of outliers at 5 months will also be evaluated (prior to breaking the blind) and sensitivity analysis will be performed on the set without outliers.

5.2.1.4 Missing Data

For the primary outcome (ODI), a measurement will be considered missing if less than 7 items in the questionnaire are answered. Otherwise, the ODI is calculated as the sum of the scores of the items that are answered, divided by the number of items answered, and multiplied by 0.2 and 100 (see appendix 17.3 in the protocol).

We will examine patterns of missingness and evaluate whether withdrawal or missing the primary endpoint is related to the outcome.

Missing data are accounted for in the linear mixed model, which is equipped to handle missing data by using all the available information on lost patients and relies on the assumption of “missing-at-random”. If there are more than 5% missing data in ODI at 5 months, sensitivity analysis will be

performed imputing the missing data with methods that do not rely on this assumption, such as last observation carried forward.

5.2.1.5 Sensitivity Analyses

1) Restricting the analysis to the PP analysis set
2) Rank based analysis (e.g. Wilcoxon rank sum test)
3) Missing data handling with different methods for imputation (see section 5.2.1.4)
4) Robustness to outliers (the patient(s) with an outlier value at 5 months will be excluded from the analysis)
5) Restrict the population to only patients with serum concentration of Infliximab >3 mg/L at 5 months follow-up in the treatment group, and all patients in the placebo group (will be done after unblinding). We will consider doing further exploratory analyses regarding concentration effect relationships using different serum infliximab cut offs.
6) Adjustment for any of the following variables that would have a clinically important imbalance at baseline (will be done after unblinding):
    a. Age
    b. LBP intensity -leg pain/sciatica
    c. Past medical history
    d. Fear-avoidance
    e. Emotional distress
    f. Physically heavy work
7) Adjustment for interaction of serum CRP level and treatment effect (if necessary a non-linear relationship will be evaluated)
8) Adjustment for interaction of duration of symptoms and treatment effect (if necessary a non-linear relationship will be evaluated)

5.2.1.6 Subgroup Analyses

The following subgroup analyses will be performed:

1. Serum CRP levels above or below cut-off. This analysis, as well as the cut-off definition, will depend on the results of the sensitivity analyses reported above (see point 6) in 5.2.1.5).
2. Inflammatory back pain, defined as at least 3 of the following 5 conditions: 1 Age of onset of back pain less than 40 years; 2 Insidious onset of back; 3 Improvement of back pain with exercise; 4 No improvement of back pain with rest; 5 Night pain with improvement upon getting up.
3. Sub-high ASAS score, including also patients with back pain starting after the age of 45. Sub-high ASAS score is defined as one of the following conditions: A and none of B-L, B plus 1 of C-L, or 2 or more of C-L. (A = MR with active (acute) inflammation highly suggestive of sacroiliitis with SpA definite radiographic sacroiliitis according to mod. New York criteria, B = HLA-B27 positive, C= Inflammatory back pain defined as at least 4 out of 5 of the conditions in point 2, D = Arthritis, E = Enthesitis, F = Dactylitis, G = Uveitis anterior, H = Psoriasis, I = Crohn's/colitis, J = Good response to NSAIDs, K = Family history of SpA, L = Elevated CRP).
4. Duration of symptoms above or below cut-off. This analysis, as well as the cut-off definition, will depend on the results of the sensitivity analyses reported above (see point 7) in 5.2.1.5).
5. Fecal calprotectin (yes/no).

Such subgroup analyses will be conducted by repeating the primary model in the different subset corresponding to the variable of interest. The subgroup effect will be tested by adding an interaction term to the primary model.

5.2.2 Dichotomous Secondary/Exploratory Outcome

5.2.2.1 Main Analysis

There is only one dichotomous outcome in this study, defined as the presence of co-interventions (defined in 5.1.4.5.) at 5 months. It is measured at baseline, at day 14, day 42, day 98, 5 months, and at 9 months. This will be analysed with logistic regression in a generalized linear mixed model. The model will include fixed effects for study site and participation to the AIM study, visit and treatment group. An interaction between treatment group and visit will be included. A random intercept for the patient ID will be used to account for repeated measurements. If fewer than 5% of the patients have participated in the AIM study, we expect it to cause problems with the convergence and model fitting, so no adjustment for this variable will be made. The analysis will be done on the FAS population.

5.2.2.2 Summary Measures

Descriptive statistics will include number and percentage of patients with co-interventions at each visit, overall and by treatment group. For the patients with co-interventions since last visit, the number of co-interventions will be summarised overall and by treatment group by mean and SD. Additionally, the concomitant medications at baseline and at 5 months will be summarised by ATC code, overall and by treatment group. Risk differences and risk ratios at 5 months will be reported as measures of treatment effect. The marginal risk difference will be estimated using average marginal means with corresponding 95% confidence intervals. Risk ratios will be estimated by using the bootstrap method.

5.2.2.3 Assumption Checks

If too many zeros are present in one treatment group at one time point, the generalized linear mixed model will present convergence issues. In such case, we will exclude the measurements taken at this time point, and only report descriptive statistics (number and percentage for each treatment group). If this is the case for more than one time point, we will use a logistic regression on the five month measurements only.

5.2.2.4 Missing Data

The generalized linear mixed model is equipped to handle missing data by relying on the assumption of “missing-at-random”. If there are more than 5% missing data in the presence of co-interventions

at 5 months, sensitivity analysis will be performed imputing the missing data with methods that do not rely on this assumption, such as "worst-case" imputation.

5.2.2.5 Sensitivity Analyses

1) Missing data with worst-case imputation
2) Chi-squared test
3) Restricting the analysis to the PP analysis set

5.2.2.6 Subgroup Analyses

The subgroups that show an effect on the primary outcome will be tested on secondary outcomes.

5.2.3 Continuous Secondary/Exploratory Outcomes

The following section applies to all continuous secondary and exploratory outcomes reported in section 5.1.5, except the change in ODI from baseline to 9 months, hours with LBP and perceived treatment. For the change in ODI from baseline to 9 months, an estimate of the treatment effect will be provided by the same model used for the primary outcome (see section 5.2.1) and calculated as average marginal effect at 9 months (with the same procedure as for the primary outcome). For hours with LBP, the number of missing records is too high, therefore we will only report descriptive statistics. For perceived treatment, the Bang Blinding Index will be calculated by treatment group at day 7, day 56, at 5 months and at 9 months, and reported with 95% confidence intervals, without further statistical analyses.

5.2.3.1 Main Analysis

The continuous secondary outcomes at different timepoints (the timepoint definition varies for different outcomes: LBP is measured every week during the first 3 months and then at 5 and 9 months, days with sick leave are measured every month up to 5 months and then at 9 months, while all other endpoints are measured at baseline, and at 3, 5 and 9 months) will be analysed with a linear mixed model, with the same adjustments and structure used in the primary outcome analysis. The analyses will be done on the FAS.

Estimates will be presented with two-sided 95% confidence intervals, and 5% significance level will be used for p-values. The treatment effect will be calculated as average marginal effect at the relevant timepoint.

5.2.3.2 Summary Measures

Descriptive statistics will be presented overall and by treatment and will include number of observations, mean value and standard deviation for each outcome. Each outcome will be plotted by visit in a longitudinal graph.

5.2.3.3 Assumption Checks

The assumption of normality will be checked. The Wilcoxon rank sum test will be conducted as sensitivity analysis to the assumption of normality.

5.2.3.4 Missing Data

For days with sick leave, health related quality of life, leg pain intensity at 5 month and at 9 months, missing measurements will be accounted for in the linear mixed model.

For LBP intensity, a measurement will be considered missing if any question is unanswered. The missing data will be accounted for in the linear mixed model.

For RMDQ, a measurement will be considered missing if less than 17 out of 24 questions are answered. Otherwise, the score will be calculated as the sum of the available answers, multiplied by 24 and divided by the number of answered questions. The missing data will be accounted for in the linear mixed model.

5.2.3.5 Sensitivity Analyses

1) Rank based analysis (e.g. Wilcoxon rank sum test)
2) Restricting the analysis to the PP analysis set

5.2.3.6 Subgroup Analyses

The subgroups that show an effect on the primary outcome will be tested on secondary outcomes.

5.2.3.7 Additional Analyses

Not applicable.

5.2.4 Ordinal Exploratory Outcomes

5.2.4.1 Main Analysis

Ordinal endpoints will be dichotomized and descriptive statistics will be reported. In addition, the global perceived effect will be analysed with a logistic model. The response variable will be the global perceived effect at 5 months, and the model will be adjusted for center, participation to the AIM study, and treatment group. If fewer than 5% of the patients have participated in the AIM

study, we expect it to cause problems with the convergence and model fitting, so no adjustment for this variable will be made.

For symptom specific well-being and patient satisfaction, the values are: 1 = ‘very satisfied’, 2 = ‘some satisfied’, 3 = ‘neither satisfied nor dissatisfied’, 4 = ‘some dissatisfied’ or 5= ‘very dissatisfied’. For global perceived effect, the values are: 1 = 'completely fine', 2 = 'much better', 3 = 'a little better', 4 = 'no change', 5= 'a little worse', 6 = 'much worse' or 7 = 'worse than ever'. Cut-off values will be 1 for symptom-specific well-being and patient satisfaction (1 vs 2-5), and 2 for the global perceived effect. (1 and 2 vs 3 to 7)

5.2.4.2 Summary Measures

Descriptive statistics will be presented overall and by treatment and will include number of observations, count and percentage for each outcome. Risk differences and risk ratios at 5 months will be reported as measures of treatment effect for the global perceived effect.

5.2.4.3 Assumption Checks

If too many zeros are present in one treatment group, we will consider a different cut-off value.

5.2.4.4 Missing Data

Worst case imputation will be used as sensitivity analysis, if more than 5% of the measurements are missing at 5 months.

5.2.4.5 Sensitivity Analyses

1) Chi-squared test or Fisher’s exact test as an alternative to the logistic model
2) Different cut-off values for the dichotomization (2 for symptom-specific well-being and patient satisfaction, 3 for the global perceived effect). These will be analysed with a logistic model.
3) Restricting the analysis to the PP analysis set

5.2.4.6 Subgroup Analyses

The subgroups that show an effect on the primary outcome will be tested on secondary outcomes.

5.2.5 Additional Analyses

Not applicable.

6 Safety Analyses

Safety analysis will include all participants who completed at least one visit. Safety analyses will be descriptive and no statistical test will be performed. Safety analysis will be provided as summary tables for AEs and laboratory tests. The safety data will be summarized by treatment group and visit.

6.1 Adverse Events

Adverse events will be coded using MedDRA, version 20.1. , graded by severity (mild, moderate, severe) and assessed for causal relationship to the study medication (unrelated, unlikely, possible, probable, definite). Information about expected AEs and serious AEs (SAEs) is reported in the protocol (section 8).

The number (%) of AE, the number (%) of mild, moderate and severe AEs, the number (%) of subjects with any AEs, with 1, 2 or > 3 AEs, and with serious AEs, all regarded as possible/probable/definite relation to study medication, will be summarised by treatment group We will further report the number (%) of subjects with any AEs, with serious AEs, and with serious unexpected and possibly related to treatment AEs (SUSAR), all irrespective of assessment of causal relationship, summarised by treatment group and visit. The number of events and number (%) of subjects with adverse events by system organ class (SOC) and preferred term (PT) will be summarised by treatment group. Percentages will be calculated using the number of patients included in the FAS as denominator. A detailed patient narrative will be given for any serious adverse event in the clinical study report in addition to listing.

6.2 Clinical Laboratory Parameters

Safety clinical laboratory parameters were collected and assessed, and used to identify adverse events (see protocol section 8.2 and 8.3). Clinical laboratory parameters (leucocytes and neutrophils) and drug concentration (after unblinding) will be summarised by treatment group and visit.

7 Statistical Software

All statistical analyses will be done in R. Version number will be included in the final report.

8 References

8.1 Literature References

1. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. Gamble et al, 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556.
2. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Van Hout et al, 2012; 15(5):708-15. doi: 10.1016/j.jval.2012.02.008.
3. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Controlled Clinical Trials 2004;25:143-56
4. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH Task Force on Research Standards for Chronic Low Back Pain. Journal of Pain 2014;15:569-85.
5. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Review of Pharmacoeconomics & Outcomes Research 2011;11:163-9

8.2 Reference to Data Handling Plan

See attachment.

8.3 Reference to the Trial Master File and Statistical Documentation

The trial TMF is stored in a secured network for research at Oslo University Hospital.

8.4 Reference to other Standard Operating Procedures or Documents

1. Gjefsen E., Bråten L.C.H., Goll G.L., et al The effect of infliximab in patients with chronic low back pain and Modic changes (the BackToBasic study): study protocol of a randomized, double blind, placebo-controlled, multicenter trial. BMC Musculoskeletal Disorders 2020; 21:698
2. Statistics Standard Operating Procedure (SOP) following NORCRIN: https://ehandboken.ous-hf.no/document/131441
3. *Trial registry ClinicalTrials.gov for BackToBasic: Infliximab in Chronic Low Back Pain and Modic Changes*. 2018; Available from: https://clinicaltrials.gov/study/NCT03704363?term=modic%20backtobasic&rank=1.

Eudract No./REC No.:	2017-004861-29 / 2017/2450
Project Name:	BackToBasic: The effect of Infliximab in patients with chronic low back pain and Modic changes. A randomized, double blind, placebo-controlled, multicenter trial
Project Short Name:	BackToBasic
Protocol version:	2.0

Distribution List

Role	Name	Address (department, e-mail, telephone)
Monitor	Kristina Schee	Research Support Services Clinical Trial Unit (CTU)
Sponsor	John-Anker Zwart	FORMI, Bygg 37B, Oslo Universitetssykehus HF Postboks 4956 Nydalen, 0424 Oslo tel. 22118621 e-mail: j.a.zwart@medisin.uio.no

Version Control

Version	Date	Description of major changes (to last version)
Draft version 0.1	14AUG2018	NA
Draft version 0.2	30JAN2019	Comments from the investigator are implemented
Final draft 0.3	05MAR2019	Comments from the investigator are implemented
Final version 1.0	25MAR2019	Updated according to final version of the eCRF

Signature List

	Role	Date	Name	Signature
Created by	Project Data Manager	14AUG2018	Kirsti Bekkedal	
Reviewed by	Data Manager	30JAN2019	Jennie-Ann Dagenborg	
Approved by	Sponsor	25MAR2019	John-Anker Zwart	

List of Abbreviations and Definitions of Terms

Abbreviation/ term	Explanation
aCRF	Annotated Case Report Form
ATC	Anatomical Therapeutic Chemical (ATC) classification system
CTU	Research Support Services, Clinical Trial Unit (CTU)
DB	Database
DEA	Data Entry Application
DEI	Data Entry Instructions
DCP	Data Control Plan
DHP	Data Handling Plan
DHR	Data Handling Report
DM	Data Management/Data Manager
DMD	Data Management Documentation
DSMB	Safety Monitoring Board
eCRF	Electronic Case Report Form
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT	Intention To Treat population
MedDRA	Medical Dictionary for Regulatory Activities
MO	Medical Officer
PDM	Project Data Manager
PL	Project Leader
PP	Per Protocol population,
PROM	Patient Reported Outcome Measurements
SAS	Statistical Analysis System language
.SAV	Statistical Package for the Social Sciences - SPSS
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Serious Adverse Reactions
UAT	User Acceptance Test document

Abbreviation/ term	Explanation
.CSV	A comma separated values file
TMF	Trial Master File

Contents

1. INTRODUCTION

1.1. Purpose

The purpose of this document is to describe the plan of action for all Data Management (DM) tasks for the BackToBasic project. This plan also identifies the documents and deliverables that will be produced as part of the DM activities. This document is managed by Project Data Manager (PDM) in this project.

2. PROJECT PERSONNEL

CTU will be responsible for the Clinical Data Management processes of this project from the first draft of the eCRF to locked database.
All Data Management personnel will be registered on Temp DM02.02 Project personnel.

3. DATA MANAGEMENT DOCUMENTATION (DMD)

3.1. Data Management Documentation

PDM will create the Data Management Documentation (DMD) according to SOP DM01. The electronic project folder is set up according to Temp DM01.01 DMD Project index. All DMD and other applicable documents created during the project will be stored in the electronic project folder, see Table 1. The electronic project folder will contain a copy of the TMF documents for this project delivered from CTU. The TMF document will be sent to the project team for archiving in the TMF consecutively.

Table 1. Dynamic References

Item	Content	Document owner
Project Index	Temp DM01.01	PDM
Project Personnel	TempDM02.02 Names, e-mail addresses and roles in the DEA in the project.	PDM
Study Overview	Temp DM04.01 Project matrix, DEA documentation, internal and external quality control (QC) and changes to the eCRF. DEA documentation is defined as a complete list of form names, variable names, with corresponding valid values, data types and labels. Functions, visibility, SDV, conditions, configuration report and annotated CRF (aCRF). aCRF is the full set of all CRF forms with variable names and complete code lists.	PDM

Item	Content	Document owner
Used Acceptance Test document (UAT)	Temp DM04.02 Intension and description of the UAT process.	PDM
DEA Approval Form	Temp DM04.02 Approval from the Principal Investigator/ Project Leader.	PDM
Changes to the DEA	Temp DM04.04 Approval during conduct if any major changes to the DEA during the study.	PDM
Data Validation Plan (DVP)	Temp DM05.01 Description of each electronic edit check and custom function edit check, and any additional manual procedure that will be performed during the validation process.	PDM
Data Validation Plan Signature Page	Temp DM05.02	PDM
Analysis population Allocation Form	Temp DM06.01 Population assignments and approval.	PDM
Database Lock Approval Form	Temp DM06.02	PDM
Locked Database Correction Form	Temp DM06.03	PDM
Database Relock Approval Form	Temp DM06.04	PDM
Randomization Request Form	Temp DM07.01 Randomization specifications according to protocol.	PDM
Code Breaking Form	Temp DM07.02 Request from the PDM to break the code.	PDM
Data Disclosure Receipt	Temp DM08.01 Electronic data transfer from the project database back to sponsor after database lock.	PDM
Approval of Coding	Temp DM10.01 Approval of the coding of Adverse Event, Medical History and Concomitant medication. *(only applicable until the approval of the coding can be performed inside the eCRF)*	PDM
Data Handling Report (DHR)	Temp DM01.03 Describes the deviations from the data management process described in the DHP and project specific procedures implemented along the project.	PDM

3.2. Protocol and Appendices

Protocol has been written by FOU, Nevroklinikken, OUS Ullevål, Att: John-Anker Zwart, professor dr.med

Protocol Identification: BackToBasic

Protocol version no. 1.0 Date: 05APR018

3.3. Case Report Form Data Entry Application (DEA)/electronic Case Report Form (eCRF) will be developed by PDM by using Viedoc™ as tool. The DEA/eCRF will be developed and tested according to SOP DM04.The ViedocMe™will be used for the Patient Reported Outcome Measurements (PROM). If there are problems with using DEA/eCRF or if the patient prefers to use paper forms, paper copies of the PROMs in the eCRF will be handed out to the patient and the data will be entered into the Viedoc™ by site personnel.

Paper Case Report Form (pCRF) will not be used in this project.

3.4. Data Validation Plan

The Data Validation Plan is a document specifying all edit checks and other quality assuring measures, including coding, taken during the data management process. It will be created by PDM, reviewed by another DM at CTU, and thereafter reviewed and approved by the PL and stored in the DMD. The DVP will be updated during conduct and when necessary. Any updates can be initiated by the project team or by the PDM. Before database (DB) lock the final version of the DVP will be approved by the PL or designee. The signed DVP signature page will be sent to TMF for archiving. A copy will be kept in the DMD folder.

3.5. DEA/eCRF documentation

The DEA/eCRF documentation will be specified are all data variables to be collected, functions, visibility, SDV, items, codelists, formats and OID's and labels. The configuration report documents the conditions and the alerts and the aCRF documents all the forms with complete code lists used in the DEA/eCRF. It will be created by PDM and reviewed by another DM at CTU. The DEA/eCRF documentation will be made by using the Viedoc™ facilities of export functionality of the content of the DEA/eCRF and be specifying special features of the DEA/eCRF.
The DEA documentation consists of the following documents:

- BackToBasic_ConfigurationReport version 1.0
- BackToBasic_OIDs and Labels version 1.0
- BackToBasic_Annotated version 1.0
- BackToBasic_Documentation version 1.0 (consist of special function and visibility in the study, SDV, Items and Codelists)
- BackToBasic_Data Validation Plan version 1.0

3.5.1. Automatic and logical checks

Illegible data will automatically be marked red during data entry in the /eCRF. Mandatory fields will be marked red in the forms and in the visit overview.
All mandatory missing data in the eCRF will be alerted, but edit checks are not run for missing data. Missing mandatory data will need an explanation made by the investigator/study nurse for the form to be accepted. The fields explained by the investigator/study nurse will not be queried by the PDM.

All invalid data, e.g. incompatible data for a date or time filed, date given in a date field which is in the future or before date of birth will be alerted. All fields marked as invalid data

during data entry, will need an explanation from the investigator to be accepted for each invalid field.

In the DVP the checks marked Viedoc is automatic at data entry. The checks marked SAS is checked in SAS manually by programming edict checks between forms and variables to identify errors. The eCRF application is programmed with numerous automatic checks which prohibit entry of invalid data. Special visibility and functions in the eCRF are specified in the sheets named Visibility and Functions in the study overview document after a needs assessment from the PDM.

3.5.2. Changes to the DEA/eCRF during the project

If the final version of the DEA/eCRF is changed after its set in production mode, the changes will be tracked in the study overview document in the sheet named Changes eCRF.

3.5.3. Project work flow

An overview of all the project visits, unscheduled events and common events in the eCRF is given in the configuration report and in the study overview document in the sheet named Study flow eCRF.

3.6. Randomization

This is a randomized, double blind, placebo-controlled study. The randomization will occur at Day 0, after all inclusion criteria are fulfilled, no exclusion criteria are fulfilled and confirmation from the radiologist that the patient can be included in the RCT MC Type I study, are completed. The patients will be randomized to placebo or infliximab. It is a block randomization with variable block size, stratified for site and participation in the AIM study or not.
The PDM has completed the Temp 07.01 Request for Randomization according to protocol. Randomization lists has been generated by Morten Valberg (CTU), using STATA 13 (StatCorp LP, College Station, TX, USA) after internal QC by Inge Christoffer Olsen (CTU). The research subject allocation will be performed in the Viedoc™ application.

4. DATA CAPTURE AND DATA FLOW PROCESS

4.1. Data Capture

4.1.1. *eCRF*

The data will be captured into Viedoc™ version 4.1

4.1.2. *Laboratory Data*

All standard laboratory samples will be analysed at the local laboratories and the results will be entered into Viedoc™.
The units and reference ranges for each local laboratory are effective from 26OCT2018 and will be loaded into Viedoc™ for each research patient. If the reference ranges changes for any site during the study a new set of reference ranges will be loaded into Viedoc™ with the new effective date. The new set of reference ranges can only be uploaded and published into Viedoc™ by the PDM.

Every laboratory results are assessed in the following categories, within normal range, not clinically significant abnormality and clinically significant abnormality.

5. DATABASE DESIGN

5.1. Creation and testing of the Data Entry Application/eCRF

The EDCS Viedoc™ will be used as DEA/eCRF. The DEA/eCRF will be designed by PDM. The project specific application will be tested by PDM, an independent DM and by the project team prior to entering of research patient data.
The result of the internal quality control (QC) is based on a needs assessment performed by the PDM and the result is documented in the study overview document in the respective sheets. Appropriate corrections according to findings are implemented in the DEA by the PDM and documented in the same document.
The result of the testing performed by the project team and following corrections will be documented in the UAT document and archived in the DMD folder. The corrections made to the DEA/eCRF after UAT are checked by the independent DM. The test data entered by the project team in the UAT site during UAT testing will be locked and kept as documentation of the QC performed by the project team.
Before the DEA is moved into production mode, Temp DM04.03 DEA Approval Form will be completed and sent to PL or designee for approval. The signed off approval form will be sent to TMF for archiving and a copy will be kept in the DMD folder.
Changes to the DEA will be documented and archived in the sheet named "Changes eCRF" in the BackToBasic overview document.

5.2. DEA training of Sponsor and Site personnel

The Project Leader or designee is responsible for the training of Sponsor and site personnel.

5.3. Data Management Annotated CRF

The annotated CRF and the database specification are made by using the Viedoc™ features of printing PDF and DB specifications. The files will be archived in the DMD.

5.4. Data Entry

There will be no data entry instruction (DEI) document made especially for this project, but an e-learning document with user specific videos is assessable before entering the DEA/eCRF and is also available at any time inside the DEA/eCRF.
Authorised site personnel will enter the data into Viedoc™, including the PROM filled out on paper by the patient, if the patient should choose not to enter the PROM data by not using ViedocMe™
Automatic logical checks will prevent the site personnel from entering data out of range and make logical errors.
No logical checks are implemented in ViedocMe™.

6. DATA QUALITY CONTROL

All specific contents of the data quality controls to be performed will be described in the project specific Data Validation Plan (DVP), Temp DM05.01. The data quality controls will

be performed after the inclusion of 20 and 100 patients and as frequently as needed before database lock.
All data quality control steps will be performed according to the SOP DM05 Data Validation.

7. SAE RECONCILIATION

Not applicable since all data are entered into Viedoc™

8. CODING

Medical coding will be performed by the PDM consecutively according to separate procedures. Items to be coded and the coding dictionaries are summarized in Table 2. Coded items will be provided to member of research team for review and approval on an ongoing basis, or at the latest when all adverse events and concomitant medications have been received and cross checked. This procedure applies until the approval of the medical coding can be performed inside the eCRF

Table 2 Coded items and coding dictionaries

Coded data items	Coding dictionary
Adverse Events	MedDRA version 22.0
Medical history	MedDRA version 22.0
Concomitant medication	ATC without DDD version 2019

9. INTERIM ANALYSIS

There is no interim analysis planned or Data Monitoring and Safety Committee (DMSC) in this study.

10. CENTRAL MONITORING

Central monitoring (CM) is checks performed on an aggregated level either per site or between sites. CM is performed with the intention to check that the collected data indicate that all sites interpret the protocol the same way and use the eCRF in a consistent manner, and that no unintended center effects make drawing conclusions from the study dubious. CM is performed with the intention to improve quality and not to evaluate the safety or efficacy of the treatment and may impact on-site monitoring. All CM will be performed according to the SOP DM12 Centralized monitoring.
The following central monitoring activities will be performed: Enrollment rate, Screen failures/enrolment, Time to data entry, Query report (rate and resolution), Error rate /deviation rate, Critical outcome variables, Deviation rate, SAE reporting: Ratio and timelines (across sites), AE reporting: Ratio (across visits), Key clinical events/visit timelines, Non Critical Outcome Variables
These checks will be described in the DVP and finding will be discussed with the monitor and statistician, if applicable. Reports will be provided to the project team every third month or more frequently depending on the data and outcome. Unpredicted events that the project team needs to be informed about could be a possible outcome.

11. DATABASE LOCK

Shortly before the planned DB lock, when most/all queries resolved and final coding has been performed, member of the research group will be informed and a database lock meeting arranged.

The PDM will create a listing of all research patients included in the project and their allocation to the different populations according to the protocol. Intention to treat (ITT) population is all randomized participants regardless of protocol adherence. Per Protocol (PP) population is all randomized patients who sufficiently comply with the protocol. Criteria for inclusion in the PP population will be specified in the statistical analysis plan, and the final criteria will be defined prior to database lock. Full analysis set (FAS) population is all randomised patients who have taken at least one dose of study medication. Safety population is all randomised patients who have taken at least one dose of study medication, i. e. identical to the FAS. If the patients are not included in a population, the cause should be listed.

The population allocation list will be provided to the Project team and approved by Project team before DB lock, using Temp DM06.01 Analysis population allocation form.
The DB will be locked after the DB lock meeting when all outstanding issues are agreed upon. Temp DM06.02 Database Lock Approval Form will be completed and sent to PL for sign off. The signed off form will be sent to TMF for archiving and a copy will be kept in the DMD folder.

11.1. Database Unlock

If any error that is required to be corrected, the database may be unlocked to correct these errors after approval from the study statistician/PL according to Temp DM06.03 Locked Database Correction Form.

12. UNBLINDING

12.1. Unblinding after Serious Unexpected Serious Adverse Reactions (SUSARs)

In case of SUSARs, the completed CIOMS form will be sent to Martha Colban (MC) according to the cooperation agreement and the project protocol. MC will complete the allocated patient treatment and forward the CIOMS form to the Competent Authority. No treatment code will be revealed to DM staff.

12.2. Unblinding after DB lock

The unblinding will be performed according to SOP DM07 Randomization and unblinding. Temp DM07.02 Code Breaking Form will be completed and the signed off form will be sent to TMF for archiving and a copy will be kept in the DMD folder.After the PDM has received the randomization list from the unblinded DM the code will be broken by merging the randomization list with the DB and the outcome is thoroughly checked.

13. DATABASE EXPORT FORMAT

The requirements of the clinical datasets that is delivered back to the sponsor after database lock are specified as SPSS files. Data will be extracted from the database as CSV – comma –

separated values with SAS script. Files extracted from the DB are listed in Table 3 and saved in a designated area (K:\Sensitivt\Forskning02\FST-DM\BackToBasic) before archiving by the sponsor.

Table 3 Files delivered to sponsor before unblinding

Name	ID
Administration of study treatment	EX.csv
Arbeidsstatus	AS.csv
ASAS	LB4.csv
Bakgrunnsvariabler	DMP.csv
Behandling siste måned	BH.csv
Blood samples	LB.csv
Blood sampling for biobank	LBGA.csv
Bloodsampling for DnR lab	LB6.csv
Clinical evaluation - neurological tests	PEN.csv
Clinical evaluation – pain provocation tests	PEP.csv
Clinical evaluation - safety	PE.csv
Co-interventions (non-pharmacological)	CMN.csv
Comments	CO.csv
Concomitant Medication	CM.csv
Demographics	DM.csv
Eligibility	EOS.csv
End of Study	EOS.csv
Forventning til behandling	PT.csv
Funksjonsbegrensninger (ODI)	ODI.csv
Funksjonsbegrensninger (RM)	RM.csv
Generell helse	GH.csv
Get randomization – Mixing nurse	GRP.csv
Graviditetstest	UA2
Helserelatert livskvalitet (EQ-5D)	EQ5D.csv
Hvordan har du det?	HSCL.csv
Inclusion/exclusion evaluation	IE.csv
Ledsagende medisinering	CMPAT.csv
Medical History	MH.csv
MRI investigator	MRI.csv
New MRI T1 and T2 - Radiologist 2	MR_2.csv
New MRI T1 and T2 - Radiologist 1	MR.csv
New MRI T1 and T2 - Radiologist 3	MR_3.csv
New MRI T1 and T2 - Radiologist 4	MR_4.csv
Om behandlingen i studien	TRT.csv
Pasienttilfredshet	PAT.csv
QOL electronic or paper	VDM.csv
Radiology assessment	IEMR.csv
Randomization	RAND.csv

Name	ID
Safety question	QS.csv
Smerte, fysisk aktivitet og jobb	FABQ.csv
Smerterapportering	NRS.csv
Tarmflorastudie	TFLK.csv
Tarmflorastudien	TF.csv
Tuberculose screening	LB3.csv
Ukentlig smerterapportering	WNRS.csv
Upload/download	UL.csv
Urine pregnancy test	UA.csv

Table 4 Files delivered to sponsor after unblinding

Name	ID
Adverse Events	AE.csv
Get randomization – Mixing nurse	GRP.csv
Anti-drug antibodies and serum drug concentration	Lb5.csv
Infliximab or placebo handling – Mixing nurse	RP.csv
Unblinding	UNB.csv

The database to be exported will be subject to quality control according SOP DM08 Electronic Data Transfer and documented in Temp DM08.01 Data Disclosure Receipt and archived in the DMD folder.

14. AUDIT

The project team will be responsible for project auditing.

15. ARCHIVING

The site will get access to download the patient data entered into the EDCS Viedcoc™ after project termination. The downloaded files will contain the complete audit trail and all queries. DMD documentation will be archived according to Temp DM01.01 and TMF document that are not sent consecutively will be sent to the project team for archiving in the TMF at the end of project. The TMF structure used in this project is described in NorCRIN SOP LM 2.05.

16. DATA HANDLING REPORT (DHR)

Deviations from the data management process described in the DHP and project specific procedures implemented along the project will be described in the DHR, Temp DM01.03